Trends in cancer risk among people with AIDS in the United States 1980–2002

Eric A. Engels[a], Ruth M. Pfeiffer[a], James J. Goedert[a], Phillip Virgo[b], Timothy S. McNeel[c], Steven M. Scoppa[c] and Robert J. Biggar[a] for the HIV/AIDS Cancer Match Study*

Background: People with AIDS have heightened cancer risk from immunosuppression. HAART has been available since 1996 and has reduced AIDS-related mortality, but there are few large-scale studies on cancer trends.

Methods: AIDS and cancer registries in 11 US regions (1980–2002) were used to identify cancers in 375 933 people with AIDS. Cancer risk relative to the general population was measured using the standardized incidence ratio (SIR), focusing on the 2 years after AIDS onset for those with AIDS in 1990–1995 and 1996–2002 (HAART era). Time trends were assessed with Poisson regression.

Results: Between 1990–1995 and 1996–2002, risk declined for the two major AIDS-defining cancers: Kaposi sarcoma [(KS) $n = 5131$; SIR, 22 100 and 3640, respectively; $P < 0.0001$] and non-Hodgkin lymphoma [(NHL) $n = 3412$; SIR, 53.2 and 22.6, respectively; $P < 0.0001$]. Declines began in the 1980s, but risk fell sharply in 1996 and was stable thereafter. Risk of cervical cancer did not change ($n = 64$; SIR, 4.2 and 5.3, respectively; $P = 0.33$). Among non-AIDS malignancies, lung cancer was most common, but risk declined between 1990–1995 and 1996–2002 ($n = 344$; SIR, 3.3 and 2.6, respectively; $P = 0.02$). Risk of Hodgkin lymphoma increased substantially over the 1990–2002 period ($n = 149$; SIR, 8.1 and 13.6, respectively; $P = 0.003$).

Conclusions: Dramatic declines in KS and NHL were temporally related to improving therapies, especially introduction of HAART, but those with AIDS remain at marked risk. Among non-AIDS-related cancers, a recent increase in Hodgkin lymphoma was observed.

AIDS 2006, **20**:1645–1654

Keywords: cancer risk, AIDS, United States, HAART

Introduction

Since the beginning of the AIDS epidemic in 1980, cancers have featured prominently as opportunistic illnesses. The two major AIDS-associated malignancies are Kaposi sarcoma (KS) and high-grade non-Hodgkin lymphoma (NHL), both of which are unambiguously increased in the setting of cellular immune deficiency and can be the initial manifestation of HIV infection defining AIDS onset [1]. Cervical cancer is less common but also considered AIDS defining in HIV-infected women [1]. Since 1996, wide availability of HAART has led to improvements in immune status among HIV-infected persons, reducing AIDS-related morbidity and prolonging survival [2–6].

Important gaps exist in our understanding of cancer risk in HIV-infected individuals. First, although several studies

From the [a]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, the [b]Computer Sciences Corporation, Rockville, Maryland, and the [c]Information Management Services, Incorporated, Silver Spring, Maryland, USA.

Correspondence to Dr E. A. Engels, Viral Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, 6120 Executive Blvd, EPS 7076, Rockville, MD 20852 USA.

E-mail: engelse@exchange.nih.gov

* See Appendix.

Received: 14 February 2006; accepted: 18 May 2006.

ISSN 0269-9370 © 2006 Lippincott Williams & Wilkins

have described dramatic declines in the occurrence of KS and NHL among HIV-infected persons and have attributed these declines to HAART [7–9], detailed data on long-term trends in cancer incidence are limited. Second, HIV-infected persons, including those who have developed AIDS, have an elevated risk for some non-AIDS-defining cancers, such as cancers of the lung, liver and anus, and Hodgkin lymphoma [7,10–14]. While these non-AIDS-defining cancers are an important source of morbidity, they have been too uncommon for small studies to evaluate thoroughly. Third, data are needed to address the concern that overall cancer incidence, which generally increases with age, will rise dramatically as people with advanced HIV infection survive longer [15].

To address these questions, population-based registry data were used to examine cancer incidence among more than 375 000 people with AIDS in the United States and to describe temporal changes in cancer incidence during 1980–2002, specifically focusing on changes in risk occurring in the HAART era (1996–2002).

Methods

HIV/AIDS and cancer registries in six US states and five metropolitan areas were linked using a probabilistic matching algorithm, utilizing registry data on name, social security number, sex, dates of birth and death, and race [16]. Legally authorized registry personnel reviewed potential matches to assess their validity. Subsequently, all identifying information was deleted from files retained for analysis. Institutional review boards at participating registries approved the study.

Previously established procedures for analyzing cancer risk among people with AIDS for specific time periods relative to AIDS onset were followed [11,12]. There are limited data on the 'AIDS onset period' (6 months before to 3 months after AIDS registration) and the analysis focused on the subsequent 2-year 'post-AIDS-onset period' (from 4 to 27 months after registration) for three reasons. First, because KS, NHL, and cervical cancer are themselves AIDS-defining conditions, it is difficult to formulate a measure of risk for the AIDS-onset period (by definition, no case of KS, NHL, or cervical cancer occurred before month 0). Second, cancer incidence in the AIDS-onset period is inflated because of the intensive clinical evaluation of the signs and symptoms of AIDS itself. Third, cancer risk after 27 months post-registration was not evaluated to minimize the effects of possible losses to follow-up owing to migration or unrecognized deaths, and those with recent AIDS onset have not yet been followed long enough to provide data on late cancer risk.

HIV/AIDS registries provided data on 407 740 people with AIDS diagnosed in 1977–2004. Those with AIDS diagnosed before 1980 ($n = 18$); those whose period of cancer risk did not overlap with a period of complete cancer registration ($n = 26\,635$), which included all those with AIDS onset in 2003–2004; and children aged 0–14 years ($n = 5154$) were excluded. These exclusions left 375 933 adult and adolescent individuals for inclusion in the study.

Invasive cancers were coded according to the *International Classification for Diseases for Oncology*, 3rd edition [17] and analyzed by site using the Surveillance, Epidemiology, and End Results (SEER) program's 'Site recode with KS and mesothelioma' [18], with the following exceptions. Some cancer subtypes (NHL, testicular cancer, kidney/renal pelvis cancer) were further assessed because of special interest generated by previous reports [11,12] or the present analyses. Also, because of small numbers, some cancer subtypes were collapsed and some rare malignancies were included with cancers of unknown site in 'other/unknown site'. Cancers at any site with poorly specified histology (codes 8000–8005; $n = 630$) were excluded because of concern that these might represent KS or NHL.

Statistical analyses

People with AIDS were grouped according to year of AIDS onset: 1980–1989 (no antiretroviral therapy or limited availability), 1990–1995 (monotherapy and dual therapy) and 1996–2002 (HAART) [5]. Demographic characteristics were compared across the three groups using χ^2 tests.

Both first and subsequent malignancies of different types were considered in analyses of cancer risk. The proportion of subjects with an AIDS-defining cancer (KS, NHL, cervical cancer) in the AIDS-onset period, identified in either the AIDS or the cancer registries was evaluated. Because these cancers are themselves AIDS-defining events, the AIDS-onset period does not provide a reliable timeframe in which to measure risk for these cancers. Therefore, only descriptive analyses to characterize broad trends over time are presented. Individuals who had developed these AIDS-defining cancers in the AIDS onset period were then excluded from the respective analyses of risk in the post-AIDS-onset period. For example, people with AIDS who had developed KS in the AIDS-onset period were deleted from the population considered at risk for KS in the post-AIDS-onset period.

For the post-AIDS-onset period, matches to the cancer registries were used to identify cancers in people with AIDS. Cancer risk in people with AIDS was described using the standardized incidence ratio (SIR), which compares incidence to that in the general population. Defined as observed cancer incidence in people with AIDS divided by the expected incidence based on population rates, SIR values were calculated for most cancer types using population incidence rates specific to

sex, age, race, calendar year and cancer registry. Because the great majority of KS and central nervous system (CNS) NHL in the general population occurs in people with AIDS, SIR values calculated using contemporaneous rates yield biased estimates of risk related to AIDS [19]. Therefore, for these two malignancies, SIR values were calculated using expected rates based on data collected by SEER registries before the AIDS epidemic (1973–1979). Exact two-sided confidence intervals (CI) were calculated.

Trends for the three AIDS-defining cancers were studied in more detail as were those non-AIDS-defining cancers where risk was elevated and changing over time. Specifically, non-AIDS-defining cancers were evaluated where the SIR was significantly elevated for those with AIDS onset in 1990–1995 or 1996–2002 and either (a) there was a significant change in SIR values between these two recent periods or (b) SIR values increased across calendar year of AIDS within the 1996–2002 period. These two criteria were evaluated using Poisson regression.

For such cancers, changes in risk over time were depicted by plotting SIR values by calendar year of AIDS onset. Fitting a piecewise linear Poisson regression model to the 1990–2002 data allowed evaluation of steady changes in risk during 1990–1995 and 1996–2002 and of a jump between these two periods. Under this model, the relative risk (RR) corresponding to the discontinuous change in 1996 is a measure of the immediate effect of availability of HAART. A change in risk in 1996 was tested by comparing the piecewise linear model with a simple linear model for a single trend over 1990–2002. (Detailed statistical methods and model results are available from the authors on request.)

Because there were few people with AIDS at the beginning of the AIDS epidemic (1980–1983), cancer risk estimates were unstable and these data are not shown in the plots of cancer risk over time. The data were also limited for 2001–2002, again reflecting trends in the US epidemic and, additionally, shorter follow-up in cancer registries. Because data from these years were used in the regression analyses, they were included in plots.

Finally, to depict the changing proportion of cancer burden attributable to various malignancies, the incidences of AIDS-defining and non-AIDS-defining cancers were plotted together as a function of calendar year of AIDS onset.

Results

Demographics of study subjects and risk of AIDS-defining cancers

Demographic characteristics of 375 933 people with AIDS included in the study are presented in Table 1. Over time, an increasing proportion were female and of non-white race/ethnicity. The age at AIDS onset increased by approximately 3 years from 1980–1989 to 1996–2002, and the proportion classified as men who had sex with men (MSM) declined.

In the AIDS-onset period, KS was reported in 25 284 (6.7%). The proportion with KS decreased beginning in the mid-1980s and continuing through the mid-1990s (declining from 25% to 2–4%); it then appeared to level off subsequently at approximately 2%. Most KS (88.7%) was identified in MSM, and the same temporal pattern was seen among MSM separately. NHL was reported in the AIDS-onset period in 8637 (2.3%). The proportion with NHL declined from approximately 3% in the late 1980s to approximately 2% in the mid-1990s and thereafter remained stable. Cervical cancer was reported in 626 (0.9%) of 71 564 females with AIDS in the AIDS-onset period. The proportion with cervical cancer was stable throughout the course of the AIDS epidemic, at approximately 1% of women with AIDS.

Cancer incidence among people with AIDS

The two most common cancers in the post-AIDS-onset period were KS and NHL (Table 2), and risks for both cancers were greatly elevated. Risk of cervical cancer was also somewhat elevated. Overall, people with AIDS had heightened risk for all non-AIDS-defining cancers combined (SIR, 2.0, 1.8 and 1.7 during 1980–1989, 1990–1995, and 1996–2002, respectively). Twelve non-AIDS-defining cancers occurred in significant excess during 1990–1995 and/or 1996–2002 (Table 2): cancers of the oral cavity/pharynx, anus, liver, larynx, lung, penis, and kidney/renal pelvis; Hodgkin lymphoma; myeloma; lymphocytic leukaemia; myeloid/monocytic leukaemia; and mesothelioma. In contrast, risks were significantly less than expected during 1990–1995 and/or 1996–2002 for cancers of the breast, prostate, urinary bladder, brain, and thyroid (Table 2).

Risk for KS declined 83.5% between 1990–1995 and 1996–2002 (SIR, 22 100 and 3640, respectively; $P < 0.0001$). The pattern was characterized by a steady decline that actually began in the 1980s and continued through 1990–1995 (Fig. 1a). There was a further fall in risk, offsetting the 1996–2002 period from the 1990–1995 period (RR, 0.41; 95% CI, 0.28–0.60). Subsequently, KS risk stayed constant during the HAART era itself. The piecewise linear model fitted the data significantly better than a linear model, providing evidence for a discrete fall in risk in 1996 (Fig. 1a). The same general pattern was seen in MSM, other men, and women (Fig. 1b).

Risk of NHL declined by 57.5% between 1990–1995 and 1996–2002 (SIR, 53.2 and 22.6, respectively; $P < 0.0001$). The overall pattern was similar to that for KS (Fig. 1c): a decline in risk beginning in the 1980s and

Table 1. Demographic characteristics of persons registered with AIDS in the United States, 1980–2002 ($n = 375\,933$).

Characteristic	AIDS diagnosis year			P value[a]
	1980–1989	1990–1995	1996–2002	
Total No.	79 387	189 129	107 417	
Sex [No. (%)]				< 0.0001
Male	70 501 (88.8)	153 733 (81.3)	80 135 (74.6)	
Female	8 886 (11.2)	35 396 (18.7)	27 282 (25.4)	
Age (years) at AIDS [No. (%)]				< 0.0001
15–29	15 135 (19.1)	28 715 (15.2)	12 856 (12.0)	
30–39	37 837 (47.7)	85 370 (45.1)	44 235 (41.2)	
40–49	18 221 (23.0)	53 541 (28.3)	34 563 (32.2)	
50+	8 194 (10.3)	21 503 (11.4)	15 763 (14.7)	
Median age at AIDS (years)	36.2	37.7	39.3	
Race/ethnicity [No. (%)]				< 0.0001
White	41 069 (51.7)	74 891 (39.6)	30 265 (28.2)	
Black	23 897 (30.1)	70 971 (37.5)	49 833 (46.4)	
Hispanic	13 658 (17.2)	41 088 (21.7)	25 591 (23.8)	
Other/unknown	763 (1.0)	2 179 (1.2)	1 728 (1.6)	
Mode of HIV exposure [No. (%)]				< 0.0001
MSM	45 576 (57.4)	83 293 (44.0)	34 888 (32.5)	
IDU	20 374 (25.7)	58 591 (31.0)	25 304 (23.6)	
MSM and IDU	5 333 (6.7)	9 683 (5.1)	3 782 (3.5)	
Heterosexual	3 216 (4.1)	19 672 (10.4)	17 486 (16.3)	
Other/unknown	4 888 (6.2)	17 890 (9.5)	25 957 (24.2)	
Registry [No. (%)]				< 0.0001
Connecticut	1 697 (2.1)	6 256 (3.3)	3 526 (3.3)	
Florida	11 693 (14.7)	35 733 (18.9)	18 494 (17.2)	
Georgia	2 690 (3.4)	8 097 (4.3)	8 758 (8.2)	
Los Angeles	10 506 (13.2)	22 276 (11.8)	13 341 (12.4)	
Massachusetts	3 244 (4.1)	8 617 (4.6)	5 923 (5.5)	
Michigan	1 784 (2.3)	6 231 (3.3)	3 393 (3.2)	
New Jersey	8 817 (11.1)	21 713 (11.5)	14 323 (13.3)	
New York City	26 474 (33.4)	57 907 (30.6)	30 873 (28.7)	
San Diego	1 685 (2.1)	5 859 (3.1)	2 758 (2.6)	
San Francisco	9 350 (11.8)	13 051 (6.9)	4 385 (4.1)	
Seattle	1 447 (1.8)	3 389 (1.8)	1 643 (1.5)	

MSM men who have sex with men; IDU injection drug use.
[a]Calculated using the χ^2 test.

continuing in 1990–1995, a fall between 1990–1995 and 1996–2002 (RR, 0.64; 95% CI, 0.48–0.85), and a stable level of risk during 1996–2002. As with KS, the piecewise linear model fitted better than a linear model. The trends in NHL risk among MSM, other men and women mirrored the overall pattern (Fig. 1d).

The patterns differed for specific histological subtypes of NHL. Risk was lower in 1996–2002 than 1990–1995 for diffuse large B cell NHL (SIR, 29.6 and 64.0, respectively; $P < 0.0001$) and its variant, immunoblastic lymphoma (SIR, 59.5 and 94.9, $P = 0.003$). In contrast, risk for Burkitt NHL changed negligibly (SIR, 52.8 and 49.5, respectively; $P = 0.74$). However, 52.0% of NHL cases were in the 'other/unspecified' histology group. Risk for other/unspecified NHL declined between 1990–1995 and 1996–2002 (Table 2). Therefore, trends in risk for NHL histological subtypes could partly reflect changes in diagnostic or coding practices.

Among NHL, 27.5% occurred in the CNS. Risk for CNS NHL fell 79.1% between 1990–1995 and 1996–2002 (SIR, 4850 and 1020, respectively; $P < 0.0001$). A decrease in risk was seen within both time periods, although the decline was not significant during 1996–2002. There was a large fall in risk between 1990–1995 and 1996–2002 (RR, 0.36; 95% CI, 0.23–0.58; Fig. 1e).

Cervical cancer risk did not change significantly between 1990–1995 and 1996–2002 (SIR, 4.2 and 5.3, respectively; $P = 0.33$). A simple linear model fitted well and showed no change over the entire period (RR per year, 1.04; 95% CI, 0.94–1.15; Fig. 1f).

Among non-AIDS-defining malignancies, only three showed changes over time as well as elevations in 1990–1995 and/or 1996–2002: lung cancer, Hodgkin lymphoma, and cancers of the kidney/renal pelvis. Lung cancer was the most common non-AIDS-defining cancer (24.2% of all cases, Fig. 2a). Following an apparent increase during the 1980s, lung cancer risk declined from 1990–1995 to 1996–2002 (SIR, 3.3 and 2.6, respectively; $P = 0.02$). A linear model fitted the 1990–2002 data well and indicated a steady decrease in lung cancer risk over this period (RR per year, 0.95; 95% CI, 0.92–0.99; Fig. 2a).

Table 2. Risk of cancer among people with AIDS in the United States, 1980–2002.[a]

Cancer type	No. cases (%)			SIR (95%CI)		
	1980–1989	1990–1995	1996–2002	1980–1989	1990–1995	1996–2002
AIDS related						
Kaposi sarcoma	2733 (63.9)	4637 (53.0)	494 (30.0)	52 900* (50 900–54 900)	22 100* (21 400–22 700)	3640* (3330–3980)
Non-Hodgkin lymphoma[b]	1115 (26.1)	2852 (32.6)	560 (34.0)	79.8* (75.2–84.6)	53.2* (51.2–55.2)	22.6* (20.8–24.6)
Burkitt NHL	38 (0.9)	88 (1.1)	39 (2.4)	57.4* (40.6–78.8)	52.8* (42.4–65.1)	49.5* (35.2–67.7)
Diffuse large B-cell NHL	485 (11.9)	1258 (14.4)	266 (16.2)	98.1* (89.6–107.3)	64.0* (60.5–67.6)	29.6* (26.1–33.3)
Immunoblastic NHL	208 (5.1)	451 (5.4)	44 (2.7)	140.5* (122.0–160.9)	94.9* (86.4–104.1)	59.5* (43.2–79.9)
Other/unspecified NHL	592 (14.5)	1506 (17.2)	255 (15.5)	70.8* (65.2–76.7)	46.6* (44.3–49.0)	17.1* (15.0–19.3)
CNS NHL	264 (6.5)	868 (10.4)	115 (7.0)	5000* (4410–5640)	4850* (4530–5180)	1020* (838–1220)
Cervix	10 (0.2)	34 (0.4)	30 (1.8)	7.7* (3.7–14.1)	4.2* (2.9–5.8)	5.3* (3.6–7.6)
Non-AIDS related						
Oral cavity and pharynx	8 (0.2)	61 (0.7)	31 (1.9)	1.2 (0.5–2.3)	2.4* (1.8–3.1)	2.1* (1.4–3.0)
Esophagus	1 (0.0)	13 (0.2)	10 (0.6)	0.4 (0.0–2.5)	1.5 (0.8–2.5)	1.9 (0.9–3.5)
Stomach	4 (0.1)	11 (0.1)	14 (0.9)	1.2 (0.3–3.2)	0.9 (0.5–1.6)	1.8 (1.0–3.0)
Small intestine	0 (0.0)	4 (0.0)	3 (0.2)	0.0 (0.0–7.4)	1.8 (0.5–4.7)	1.9 (0.4–5.5)
Colon and rectum	11 (0.3)	37 (0.4)	36 (2.2)	0.9 (0.4–1.6)	0.8 (0.5–1.1)	1.0 (0.7–1.4)
Anus	11 (0.3)	53 (0.6)	43 (2.6)	18.3* (9.1–32.7)	20.7* (15.5–27.0)	19.6* (14.2–26.4)
Liver	3 (0.1)	27 (0.3)	20 (1.2)	2.4 (0.5–7.1)	4.0* (2.6–5.8)	3.3* (2.0–5.1)
Pancreas	2 (0.0)	6 (0.1)	5 (0.3)	0.8 (0.1–3.0)	0.6 (0.2–1.4)	0.7 (0.2–1.7)
Larynx	5 (0.1)	18 (0.2)	16 (1.0)	1.7 (0.5–3.9)	1.7* (1.0–2.8)	2.7* (1.6–4.4)
Lung	49 (1.2)	233 (2.8)	111 (6.7)	2.5* (1.9–3.3)	3.3* (2.9–3.8)	2.6* (2.1–3.1)
Bones and joints	1 (0.0)	2 (0.0)	0 (0.0)	1.8 (0.0–9.8)	1.0 (0.1–3.6)	0.0 (0.0–3.6)
Soft tissue including heart	3 (0.1)	9 (0.1)	3 (0.2)	1.9 (0.4–5.7)	1.5 (0.7–2.9)	0.8 (0.2–2.4)
Melanoma of the skin	8 (0.2)	25 (0.3)	12 (0.7)	1.2 (0.5–2.3)	1.2 (0.8–1.8)	1.0 (0.5–1.8)
Breast	0 (0.0)	14 (0.2)	28 (1.7)	0.0* (0.0–0.7)	0.4* (0.2–0.6)	0.8 (0.5–1.2)
Uterus	0 (0.0)	3 (0.0)	2 (0.1)	0.0 (0.0–7.7)	0.7 (0.1–2.1)	0.5 (0.1–1.7)
Ovary	1 (0.0)	2 (0.0)	1 (0.1)	1.9 (0.0–10.4)	0.5 (0.1–1.9)	0.3 (0.0–1.9)
Vagina and vulva	0 (0.0)	3 (0.0)	3 (0.2)	0.0 (0.0–33.0)	4.2 (0.9–12.3)	4.4 (0.9–12.8)
Prostate	8 (0.2)	39 (0.5)	36 (2.2)	0.9 (0.4–1.8)	0.5* (0.4–0.7)	0.5* (0.4–0.7)
Testis	11 (0.3)	22 (0.3)	5 (0.3)	2.0 (1.0–3.5)	1.5 (0.9–2.2)	0.7 (0.2–1.6)
Testis seminoma	9 (0.2)	15 (0.2)	4 (0.2)	2.6* (1.2–4.9)	1.6 (0.9–2.6)	0.8 (0.2–2.1)
Penis	0 (0.0)	5 (0.1)	4 (0.2)	0.0 (0.0–14.0)	5.6* (1.8–13.1)	8.0* (2.2–20.6)
Urinary bladder	0 (0.0)	9 (0.1)	0 (0.0)	0.0* (0.0–0.8)	0.7 (0.3–1.3)	0.0* (0.0–0.5)
Kidney and renal pelvis	6 (0.1)	19 (0.2)	21 (1.3)	1.6 (0.6–3.5)	1.2 (0.7–1.9)	1.8* (1.1–2.8)
Renal cell carcinoma	2 (0.0)	15 (0.2)	15 (0.9)	0.8 (0.1–2.7)	1.3 (0.7–2.1)	1.9* (1.1–3.2)
Brain	13 (0.3)	4 (0.0)	3 (0.2)	3.7* (2.0–6.4)	0.4* (0.1–0.9)	0.5 (0.1–1.4)
Thyroid	4 (0.1)	3 (0.0)	4 (0.2)	1.9 (0.5–4.7)	0.3* (0.1–0.9)	0.5 (0.1–1.4)
Hodgkin lymphoma	24 (0.6)	77 (0.9)	72 (4.4)	7.0* (4.5–10.4)	8.1* (6.4–10.1)	13.6* (10.6–17.1)
Myeloma	4 (0.1)	15 (0.2)	11 (0.7)	2.7 (0.7–7.0)	2.2* (1.2–3.6)	2.2* (1.1–3.9)
Lymphocytic leukemia	1 (0.0)	7 (0.1)	1 (0.1)	1.2 (0.0–6.9)	2.7* (1.1–5.6)	0.7 (0.0–4.1)
Myeloid and monocytic leukemia	7 (0.2)	11 (0.1)	11 (0.7)	3.1* (1.2–6.4)	1.3 (0.7–2.4)	2.2* (1.1–4.0)
Mesothelioma	0 (0.0)	5 (0.1)	2 (0.1)	0.0 (0.0–11.0)	4.5* (1.5–10.5)	3.4 (0.4–12.2)
Other/unknown site[c]	37 (0.9)	105 (1.3)	55 (3.3)	5.1* (3.6–7.1)	4.1* (3.3–4.9)	3.4* (2.5–4.4)
All non-AIDS-associated cancers	222 (5.4)	842 (10.1)	563 (34.2)	2.0* (1.7–2.3)	1.8* (1.7–1.9)	1.7* (1.6–1.9)

NHL, non-Hodgkin lymphoma; SIR, standardized incidence ratio; CI, confidence interval; CNS, central nervous system.
[a]Cancers are from the 2–year period 4–27 months after AIDS onset, referred to as the post-AIDS period. For this period, 317 428 people with AIDS (60 485 females) provided data on cancer risk, yielding 477 368 person-years of follow-up (92 377 person-years in females). The numbers at risk for AIDS-defining cancers in the post-AIDS-onset period were slightly smaller (295 390 for KS, 311 538 for NHL, 59 907 for cervical cancer) because of exclusion of individuals who had these cancers in the AIDS-onset period.
[b]Among non-Hodgkin lymphomas in the 'other/unspecified' category, 2091 (88.9%) were of unspecified subtype, while the remainder were other specified subtypes. The category 'central nervous system non-Hodgkin lymphomas' includes lymphomas in the various histological categories.
[c]Among cancers of other/unknown site, 124 (62.9%) were of unknown site.
*$P < 0.05$.

Hodgkin lymphoma was the second most common non-AIDS-defining malignancy (10.6% of all cases) and showed a different pattern (Fig. 2b) in that risk was 68% higher in 1996–2002 than 1990–1995 (SIR, 13.6 and 8.1, respectively; $P = 0.003$). A linear model was a good fit to these data and indicated a rise over the entire 1990–2002 period (RR per year, 1.09; 95% CI, 1.04–1.13; Fig. 2b).

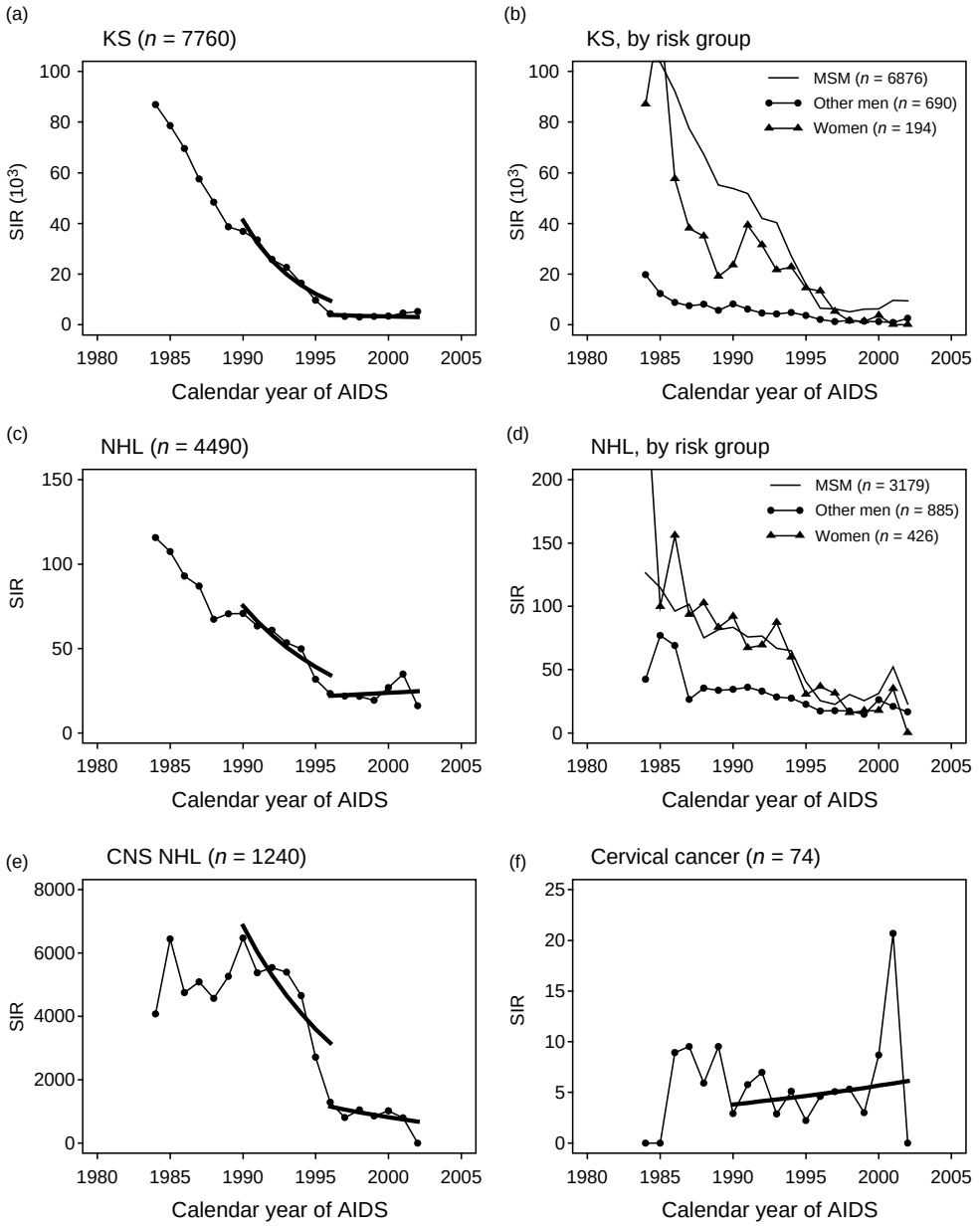

Fig. 1. Risks of AIDS-defining malignancies in the post-AIDS-onset period by calendar year of AIDS onset (1984–2002) and for various AIDS risk groups (men who had sex with men, other men, women). (a) Kaposi sarcoma; (b) Kaposi sarcoma by AIDS risk group; (c) non-Hodgkin lymphoma; (d) non-Hodgkin lymphoma by AIDS risk group; (e) central nervous system non-Hodgkin lymphoma; (f) cervical cancer. The number of outcomes above each panel or within the panel refers to cancers arising in people with AIDS onset in 1984–2002; the total number of outcomes for 1980–2002 was slightly larger (Table 2). Risk is presented as the standardized incidence ratio (SIR). The observed SIR values are presented. Additionally, SIR values from the piecewise linear Poisson regression model are shown as a thick solid line (a,c,e); the fall between the two segments of the thick solid line corresponds to the discontinuous change in risk in 1996, a measure of the immediate effect of availability of HAART. (f) The piecewise linear model (not shown) did not fit better than a simpler linear model for a single trend across 1990–2002 (thick solid line).

Risk for kidney/renal pelvis cancer increased non-significantly from 1990–1995 to 1996–2002 (SIR, 1.2 and 1.8, respectively; $P = 0.19$). Overall, 42 (91%) of these cancers were in the kidney parenchyma, of which 32 (76%) were renal cell carcinomas. Risk specifically for renal cell carcinoma increased from 1990–1995 to 1996–2002 (SIR, 1.3 and 1.9, respectively; $P = 0.26$). Figure 2c,d shows the trends for kidney/renal pelvis cancers and renal cell carcinoma. Risk for renal cell carcinoma increased steeply during the 1996–2002 period (RR per year, 1.54; 95% CI, 1.09–2.18). Notably, the high SIR values for renal cell carcinoma in 2001 and 2002 (Fig. 2d) were each the result of only a single observed case. An increasing trend across the HAART era

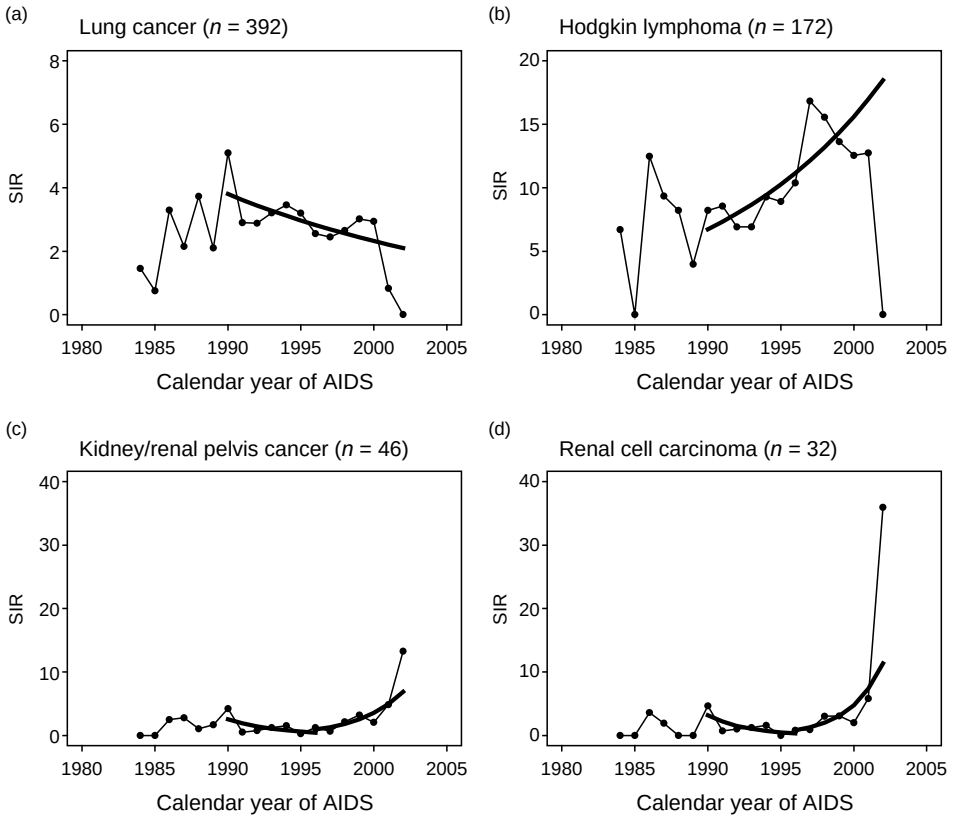

Fig. 2. Risk of selected non-AIDS-defining malignancies in the post-AIDS-onset period by calendar year of AIDS onset (1984–2002). (a) lung cancer; (b) Hodgkin lymphoma; (c) kidney and renal pelvis cancer; (d) renal cell carcinoma. The number of outcomes above each panel refers to cancers arising in people with AIDS onset in 1984–2002; the total number of outcomes for 1980–2002 was slightly larger (Table 2). Risk is presented as the standardized incidence ratio (SIR). SIR estimates from a simple linear Poisson model are presented as a thick solid line (a,b); estimates from piecewise linear models are shown as thick solid lines (c,d).

was still suggested when data from 2001–2002 were excluded, but this was no longer statistically significant (RR per year, 1.42; 95% CI, 0.88–2.28).

Finally, the proportion of total cancer incidence attributable to AIDS-defining and non-AIDS-defining cancers over time is depicted in Fig. 3. As a result of declines in KS and NHL incidence, non-AIDS-defining cancers made up an increasing proportion of cancers over time (i.e., 10.1% in 1990–1995 and 34.2% in 1996–2002).

Discussion

Our study provides population-based data on long-term trends in cancer incidence among people with AIDS. We have documented dramatic declines for the two major AIDS-defining malignancies, KS and NHL. Their steadily decreasing incidence before the HAART era is a remarkable feature of these trends and may have several explanations. For example, the declines in the early 1990s might reflect widening use of single and dual antiretroviral drug regimens [2,3,5,20]. Expansions of the AIDS definition in 1987 and 1993 [1,21], which led to AIDS being diagnosed in people with less immunosuppression, could also partly explain the declines.

The most likely explanation for the further sharp fall in KS and NHL incidence in 1996 is the introduction of HAART. Already by the end of 1996, half of those with AIDS in the United States who were under medical care had started HAART [22]. The decrease in risk at the start of the HAART era appeared greatest for CNS NHL and KS, and somewhat smaller for NHL overall, corroborating previous observations [7–9].

Our data are the first to indicate clearly that risk for AIDS-defining cancers has not continued to decline during the HAART era. During this period, HAART use increased [22] and physicians became more experienced with antiretroviral regimens, which included successively more potent agents, such as efavirenz and lopinavir/ritonavir. However, introduction of new antiretroviral agents was promptly followed by increased HIV drug resistance, especially among those who had developed AIDS [23,24]. Additionally, because HAART is

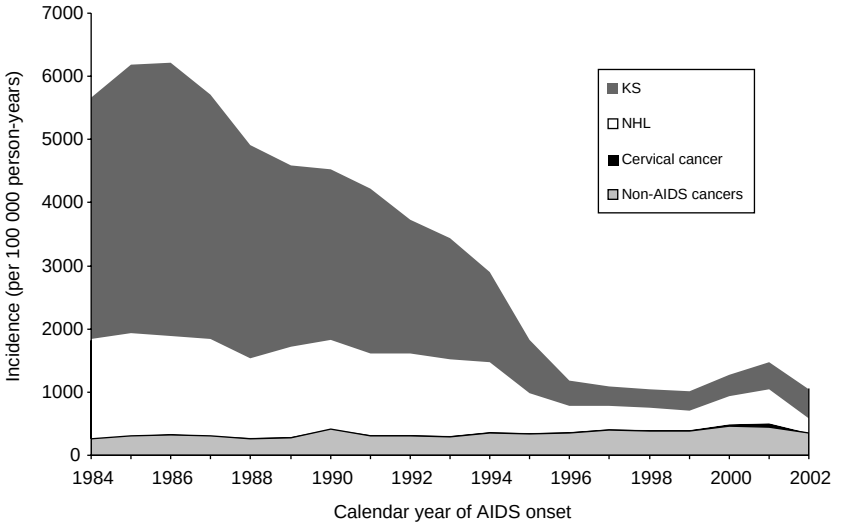

Fig. 3. Cancer incidence among people with AIDS in the United States (1984–2002). Incidence is shown as a function of calendar year of AIDS onset for Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), cervical cancer, and non-AIDS-defining cancers. Incidence estimates for each cancer are stacked on top of each other to depict the proportion of total cancer incidence contributed by each cancer type. Analysis was restricted to the 2-year period 4–27 months after AIDS onset.

extremely effective in preventing AIDS, many people who develop AIDS in the HAART era have had difficulty accessing medical care or complying with medical regimens. Continuing elevations in risk for KS and NHL among those with AIDS may, therefore, reflect difficulty engaging medical care or HIV drug resistance.

Cervical cancer risk did not change over time, confirming observations in smaller studies [7,8]. Elevated cervical cancer risk among women with AIDS results from frequent infection with oncogenic human papillomavirus (HPV) subtypes, lack of clearance of HPV, and frequent progression to early-stage neoplastic lesions [25,26]. The flat trend for cervical cancer suggests that HAART-induced immune reconstitution has little effect on progression through later stages of HPV-induced neoplasia [27].

SIR values for most non-AIDS-defining cancers did not change over time. Nonetheless, because of declines in KS and NHL, non-AIDS-defining malignancies now make up approximately a third of all cancers among people with AIDS (Fig. 3). Lung cancer was the most common non-AIDS-defining cancer and occurred at significant excess. Previous studies have reported an elevated risk of lung cancer in HIV-infection [7,10–12,28–30], with inconclusive results regarding possible changes over time or relationship to HAART use [7,28–30]. A high prevalence of smoking accounts for much of the elevated risk, but it remains unclear whether other factors are also involved.

Hodgkin lymphoma occurs in excess among people with AIDS [10–12]. We found a substantial increase over time, which was best described as a steady rise across 1990–2002, although limited data precluded a clear conclusion regarding the most recent trend. Two prior studies reported an increase in Hodgkin lymphoma incidence over time and suggested an association with HAART use [7,14]. We hypothesize that increasing risk of Hodgkin lymphoma could reflect immune-modulating effects of antiretroviral therapy. Although Hodgkin lymphoma risk has risen, this malignancy is still less common than NHL among people with AIDS.

Renal cell carcinoma was the only other malignancy to show a recent rise. This finding was unexpected and based on few cases, so it should be treated with some caution. One previous study reported an increase in kidney cancer in the HAART era [14], but others did not [7,13]. Risk for renal cell carcinoma is elevated among patients with end-stage renal disease [31], and it is possible that kidney disease caused by HIV or medications [32] is contributing to the recent increase in renal cell carcinoma.

Our study's strengths include its large size, inclusion of all HIV risk groups, and coverage of major geographic centers of the United States AIDS epidemic over its entire duration. There are also limitations. First, we did not study individuals with early-stage HIV infection. Nonetheless, we expect that cancer risk would generally be lower among HIV-infected persons without AIDS, because of their better immune status. Second, we had no data on an individual level regarding antiretroviral use. Our study, therefore, used an ecological approach, attributing changes over time to improving antiretroviral regimens [5]. Third, we had no data on other cancer cofactors, such as viral infections or tobacco use, cancer screening, or access to care. Changes in these factors could have affected time trends.

In conclusion, our study illustrates dramatic population-level benefits provided by HAART in preventing KS and NHL. Nonetheless, risk for these cancers in those with AIDS remains markedly elevated compared with the general population. Continued monitoring of trends in cancer risk will be important.

Acknowledgements

We are grateful for the many staff members at the registries who collected the data, prepared data files for the matches and facilitated the record linkages. We also thank our study managers Norma Kim and Emily Moser (RTI International, Rockville, Maryland).

Sponsorship: This research was supported by the Intramural Research Program of the National Cancer Institute, National Institutes of Health.

References

1. Centers for Disease Control. **1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults.** *MMWR Morb Mortal Wkly Rep* 1992; **41**:1–19.
2. Mocroft A, Vella S, Benfield TL, Chiesi A, Miller V, Gargalianos P, *et al*. **Changing patterns of mortality across Europe in patients infected with HIV-1.** *Lancet* 1998; **352**:1725–1730.
3. Detels R, Tarwater P, Phair JP, Margolick J, Riddler SA, Munoz A. **Effectiveness of potent antiretroviral therapies on the incidence of opportunistic infections before and after AIDS diagnosis.** *AIDS* 2001; **15**:347–355.
4. Centers for Disease Control and Prevention. Update: AIDS: United States, 2000. *MMWR Morb Mortal Wkly Rep* 2002; **51**:592–595.
5. Tarwater PM, Mellors J, Gore ME, Margolick JB, Phair J, Detels R, *et al*. **Methods to assess population effectiveness of therapies in human immunodeficiency virus incident and prevalent cohorts.** *Am J Epidemiol* 2001; **154**:675–681.
6. Sterne JAC, Hernan MA, Ledergerber B, Tilling K, Weber R, Sendi P, for the Swiss HIV Cohort Study. **Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study.** *Lancet* 2005; **366**: 378–384.
7. Clifford GM, Polesel J, Rickenbach M, Dal Maso L, Keiser O, Kofler A, *et al*. **Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy.** *J Natl Cancer Inst* 2005; **97**: 425–432.
8. International Collaboration on HIV and Cancer. **Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults.** *J Natl Cancer Inst* 2000; **92**:1823–1830.
9. Ledergerber B, Egger M, Erard V, Weber R, Hirschel B, Furrer H, *et al*. **AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy. The Swiss HIV Cohort Study.** *JAMA* 1999; **282**:2220–2226.
10. Grulich AE, Wan X, Law MG, Coates M, Kaldor JM. **Risk of cancer in people with AIDS.** *AIDS* 1999; **13**:839–843.
11. Frisch M, Biggar RJ, Engels EA, Goedert JJ. **Association of cancer with AIDS-related immunosuppression in adults.** *JAMA* 2001; **285**:1736–1745.
12. Goedert JJ, Coté TR, Virgo P, Scoppa SM, Kingma DW, Gail MH, *et al*. **Spectrum of AIDS-associated malignant disorders.** *Lancet* 1998; **351**:1833–1839.
13. Hessol NA, Seaberg EC, Preston-Martin S, Massad LS, Sacks HS, Silver S, *et al*. **Cancer risk among participants in the Women's Interagency HIV Study.** *J Acquir Immune Defic Syndr* 2004; **36**:978–985.
14. Herida A, Mary-Krause M, Kaphan R, Cadranel J, Poizot-Martin I, Rabaud C, *et al*. **Incidence of non-AIDS-defining cancers before and during the highly active antiretroviral therapy era in a cohort of human immunodeficiency virus-infected patients.** *J Clin Oncol* 2003; **21**:3447–3453.
15. Engels EA, Goedert JJ. **Human immunodeficiency virus/acquired immunodeficiency syndrome and cancer: past, present, and future.** *J Natl Cancer Inst* 2005; **97**:407–409.
16. Jaro MA. **Probabilistic linkage of large public health data files.** *Stat Med* 1995; **14**:491–498.
17. World Health Organization. International *Classification of Diseases for Oncology*, 3rd edn. Geneva: World Health Organization; 2000.
18. National Cancer Institute. *SEER Cancer Statistics Review, 1975–2002*. Bethesda, MD: National Cancer Institute; 2005.
19. Jones ME, Swerdlow AJ. **Bias in the standardized mortality ratio when using general population rates to estimate expected number of deaths.** *Am J Epidemiol* 1998; **148**:1012–1017.
20. Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, for the HIV Outpatient Study Investigators. **Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection.** *N Engl J Med* 1998; **338**: 853–860.
21. Centers for Disease Control. **Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome.** *MMWR Morb Mortal Wkly Rep* 1987; **36(Suppl 1)**:1S–15S.
22. Cunningham WE, Markson LE, Andersen RM, Crystal SH, Fleishman JA, Golin C, for the HCSUS Consortium. **Prevalence and predictors of highly active antiretroviral therapy use in patients with HIV infection in the United States.** *J Acquir Immune Defic Syndr* 2000; **25**:115–123.
23. Richman DD, Morton SC, Wrin T, Hellmann N, Berry S, Shapiro MF, *et al*. **The prevalence of antiretroviral drug resistance in the United States.** *AIDS* 2004; **18**:1393–1401.
24. Mocroft A, Ledergerber B, Viard JP, Staszewski S, Murphy M, Chiesi A, for the EuroSIDA Study Group. **Time to virological failure of 3 classes of antiretrovirals after initiation of highly active antiretroviral therapy: results from the EuroSIDA Study Group.** *J Infect Dis* 2004; **190**:1947–1956.
25. Harris TG, Burk RD, Palefsky JM, Massad LS, Bang JY, Anastos K, *et al*. **Incidence of cervical squamous intraepithelial lesions associated with HIV serostatus, CD4 cell counts, and human papillomavirus test results.** *JAMA* 2005; **293**: 1471–1476.
26. Strickler HD, Burk RD, Fazzari M, Anastos K, Minkoff H, Massad LS, *et al*. **Natural history and possible reactivation of human papillomavirus in human immunodeficiency virus-positive women.** *J Natl Cancer Inst* 2005; **97**:577–586.
27. Frisch M, Biggar RJ, Goedert JJ. **Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome.** *J Natl Cancer Inst* 2000; **92**:1500–1510.
28. Dal Maso L, Polesel J, Serraino D, Franceschi S. **Lung cancer in persons with AIDS in Italy, 1985–1998.** *AIDS* 2003; **17**:2117–2119.
29. Bower M, Powles T, Nelson M, Shah P, Cox S, Mandelia S, *et al*. **HIV-related lung cancer in the era of highly active antiretroviral therapy.** *AIDS* 2003; **17**:371–375.
30. Engels EA, Brock MV, Chen J, Hooker CM, Gillison M, Moore RD. **Elevated incidence of lung cancer among HIV-infected individuals.** *J Clin Oncol* 2006; **24**:1383–1388.
31. Stewart JH, Buccianti G, Agodoa L, Gellert R, McCredie MR, Lowenfels AB, *et al*. **Cancers of the kidney and urinary tract in patients on dialysis for end-stage renal disease: analysis of data from the United States, Europe, and Australia and New Zealand.** *J Am Soc Nephrol* 2003; **14**:197–207.
32. Kimmel PL, Barisoni L, Kopp JB. **Pathogenesis and treatment of HIV-associated renal diseases: lessons from clinical and animal studies, molecular pathologic correlations, and genetic investigations.** *Ann Intern Med* 2003; **139**:214–226.

Appendix

HIV/AIDS and cancer registries in the following regions participated in the HIV/AIDS Cancer Match Study: the states of Connecticut, Florida, Georgia, Massachusetts, Michigan and New Jersey; and the metropolitan areas of Los Angeles, San Diego and San Francisco (California), New York City (New York) and Seattle (Washington).